CLAIMS

1. A method for improving the effect of an anti-cancer therapy in a patient, the method comprising increasing the susceptibility of malignant cells in the patient to said anti-cancer therapy without substantially increasing the susceptibility of non-malignant cells to said anti-cancer therapy.

2. The method according to claim 1, comprising effecting inhibition of the anti-apoptotic effect of a protease inhibitor activity of at least one protease inhibitor in the patient, thereby increasing the susceptibility of malignant cells to said anti-cancer therapy relative to the susceptibility of non-malignant cells to said anti-cancer therapy.

3. The method according to claim 2, wherein inhibition is achieved by administering a blocker of the *in vivo* anti-apoptotic action of a protease inhibitor to the patient.

4. The method according to claim 3, wherein the protease inhibitor is a serine protease inhibitor, is an inhibitor of a metalloprotease, is an inhibitor of a cysteine protease (thiol protease), is an inhibitor of an aspartic protease, is an inhibitor of any other protein degrading enzyme, is an inhibitor of a heperanase or is an inhibitor of any other enzyme participating in degradation of the extracellular matrix, and preferably the protease inhibitor is selected from the group consisting of PAI-1, PAI-2, PAI-3, Protease Nexin 1, TIMP-1, TIMP-2, TIMP-3, TIMP-4, Stephin A, Stephin B, and Cystatin C.

5. The method according to claim 3 or 4, wherein the blocker is selected from the group consisting of a polyclonal antibody, a monoclonal antibody, an antibody fragment, a soluble receptor, a low molecular molecule, a natural products, a peptide, an anti-sense polynucleotide, a ribozyme, and a mimic of an antisense polynucleotide such as an anti-sense LNA or PNA molecule.

6. The method according to any one of claims 3-5, wherein the blocker is administered prior to instigation of the anti-cancer therapy.

7. The method according to any one of claims 3-6, wherein the blocker is administered at the onset or during the anti-cancer therapy.

8. The method according to any one of claims 3-7, wherein the blocker is administered as part of a pharmaceutical composition that includes a pharmaceutically acceptable carrier, vehicle or diluent.

9. The method according to claim 8, wherein the pharmaceutical composition is in a dosage form selected from the group consisting of an oral dosage form; a buccal dosage form; a sublingual dosage form; an anal dosage form; and a parenteral dosage form such as an intravenous, an intra-arterial, an intraperitoneal, a subdermal, an intradermal, an intramuscular, and an intracranial dosage form.

10. The method according to claim 8 or 9, wherein administration is via a route selected from the group consisting of the parenteral route such as the intradermal, the subdermal, the intra-arterial, the intravenous, and the intramuscular route; the peritoneal route; the oral route; the buccal route; the sublinqual route; the epidural route; the spinal route; the anal route; and the intracranial route

11. The method according to any one of the preceding claims, wherein the anti-cancer therapy comprises subjecting the patient to conditions that induce cell death by apoptosis.

12. The method according to any one of the preceding claims, wherein the increase in susceptibility of the malignant cells is the consequence of a preferential increase in apoptosis in the malignant cells that are subjected to the anti-cancer therapy.

13. The method according to any one of the preceding claims, wherein the anti-cancer therapy is supplemented with treatment of the patient with an anti-cancer drug, the efficacy of which does not depend on expression of protease inhibitors in the tumour tissue.

14. The method according to any one of the preceding claims, wherein the anti-cancer therapy is selected from the group consisting of radiation therapy, endocrine therapy, and cytotoxic or cytostatic chemotherapy, immunotherapy, treatment with biological response modifiers, treatment with protein kinase inhibitors, or a combination thereof.

15. The method according to claim 14, wherein the cytotoxic or cytostatic chemotherapy is selected from the group consisting of treatment with alkylating agents, topoisomerase inhibitors type 1 and type 2, antimetabolites, tubulin inhibitors, platinoids, and taxanes.

16. The method according to claim 14, wherein the endocrine therapy is treatment with antiestrogens, aromatase inhibitors, inhibitors of gonadotropins, antiandrogens, antiprogestins, or combinations thereof.

17. The method according to any one of the preceding claims, wherein the anti-cancer therapy targets a malignant neoplasm selected from the group consisting of malignant brain tumour, malignant melanoma, sarcoma, head and neck cancer, gastrointestinal cancer such as

gastric, pancreatic, colon, and rectum cancer, carcinoides, lung cancer, breast cancer, gynecological cancer, such as ovary, cervix uteri, and corpus uteri cancer, and urological cancers, such as prostate, renal, and bladder cancer.

18. The method according to claim 17, wherein elevated protease inhibitor expression is correlated with poor prognosis.

19. A method for predicting whether a cancer patient will benefit from an anti-cancer therapy, where the efficiency of said anti-cancer therapy depends on tumour tissue expression of protease inhibitors, the method comprising determining whether cells from tumour tissue in the patient expresses any one of a number of preselected protease inhibitors, and establishing that the patient will not benefit from the anti-cancer therapy if any one of said protease inhibitors is expressed beyond a relevant threshold value and establishing that the patient will benefit from the anti-cancer therapy if none of the preselected protease inhibitors are expressed beyond their relevant threshold values.

20. The method according to claim 19, wherein the preselected protease inhibitors are selected from the group consisting of the protease inhibitors defined in claim 4.

21. The method according to claim 19 or 20, wherein determination of whether cells from tumour tissues in the patient expresses any one of the number of preselected protease inhibitors is performed by measuring on a sample selected from the group consisting of a tumour tissue sample, a blood sample, a plasma sample, a serum sample, a urine sample, a faeces sample, a saliva sample, and a sample of serous liquid from the thoracic or abdominal cavity.

22. The method according to claim 21, wherein measuring is performed by means of DNA level measurement, mRNA level measurement such as *in situ* hybridization, Northern blotting, QRT-PCR, and differential display, and protein level measurement, such as Western blotting, Immunohistochemistry, ELISA, and RIA.

23. The method according to any one of claims 19-22, wherein the anti-cancer therapy induces cell death by apoptosis.

24. The method according to claim 22, wherein measuring is performed by means of DNA level measurement or protein level measurement and performed on archive material from the patient, such as a paraffin block comprising tumour tissue.

25. The method according to claim 24, wherein the DNA level measurement is selected from fluorescent in situ hybridization and chromogenic in situ hybridization.

26. The method according to claim 25, wherein the protein level measurement is immunohistochemistry.

27. A method for anti-cancer treatment of a cancer patient, the method comprising predicting, according to the method of any one of claims 19-26, whether the cancer patient will benefit from an anticancer therapy, where the efficiency of said anti-cancer therapy depends on tumour tissue expression of protease inhibitors, and subsequently
a) subjecting the patient to the anticancer therapy if the prediction provides a positive answer, or
b) subjecting the patient to the improved cancer therapy according to any one of claims 1-18, if the prediction provides a negative answer.

28. A method for anti-cancer treatment of a cancer patient, the method comprising monitoring a patient undergoing an existing anti-cancer therapy, wherein the monitoring is performed by repeatedly exercising the prediction according to the method of any one of claims 19-23, whether the patient will continue to benefit from the existing anticancer therapy, and
a) continuing subjecting the patient to the anticancer therapy if the prediction in the monitoring provides a positive answer, or
b) switching the patient to another anticancer therapy by means of the method according to any one of claims 1-18, if the prediction in the monitoring provides a negative answer.

29. The method according to claim 27 or 28, wherein the anti-cancer therapy is selected from neoadjuvant therapy, adjuvant therapy, and therapy of metastatic disease.

30. A method for identifying an agent that blocks the anti-apoptotic effect of a protease inhibitor, the method comprising
- providing a first population of malignancy-derived cells that are +/+ or +/- for said protease inhibitor or where the protease inhibitor is provided from an external source,
- providing a second population of malignancy-derived cells that are -/- for said protease inhibitor,
- subjecting samples of said first and second populations of cells to substantially the same apoptosis-inducing conditions in the absence and presence of a defined concentration of a candidate agent,
- determining the degree of apoptosis induced in said samples, and
- identifying the candidate agent as an agent that blocks the anti-apoptotic effect of the protease inhibitor if 1) the degree of apoptosis induced in the samples from the first population of cells is significantly higher in the presence of the candidate agent, and 2) the degree of apoptosis induced in the samples from the second population of cells is not significantly higher in the presence of the candidate agent.

31. The method according to claim 30, wherein different defined concentrations of the candidate agent are tested, optionally in parallel.

32. The method according to claim 30 or 31, wherein the result is subsequently confirmed by reverting -/- cells into +/- or +/+ cells and establishing that the reverted cells' susceptibility to apoptosis can be significantly increased by the candidate agent.

33. The method according to any one of claims 30-32, wherein the first population of cells is less susceptible to the apoptosis-inducing conditions than the second population in the absences of the candidate agent.

34. The method according to any one of claims 27-33, wherein the samples of the first and second population of cells are grown in an experimental animal.

35. The method according to any one of claims 27-33, wherein the samples of the first and second population of cells are grown in culture.

36. The method according to claim 34, wherein the degree of adverse effects in the animal is also determined.

37. A method for identifying an agent that blocks the anti-apoptotic effect of a protease inhibitor, the method comprising
- providing a first population of malignancy-derived cells that are +/+ or +/- for said protease inhibitor or where the protease inhibitor is provided from an external source,
- implanting the first population of cells in an experimental animal and allowing them to grow,
- subjecting the animal to apoptosis-inducing conditions in the absence and presence of a defined concentration of a candidate agent,
- determining the degree of tumour development and/or progression in said animal,
- determining the degree of apoptosis-related adverse effects in the animal, and
- identifying the candidate agent as an agent that blocks the anti-apoptotic effect of the protease inhibitor if 1) the degree of tumour development is significantly lower in the presence of the candidate agent, and 2) the degree of apoptosis-related adverse effects induced is not significantly higher in the presence of the candidate agent.

38. A method for identifying an anti-cancer treatment the efficacy of which is dependent on presence or absence of apoptosis-inhibiting protease inhibitors, the method comprising
- providing a first population of malignancy-derived cells that are +/+ or +/- for said protease inhibitor,

- providing a second population of malignancy-derived cells that are -/- for said protease inhibitor,
- subjecting samples of said first and second populations of cells to substantially the same anti-cancer treatment in the absence and presence of an effective concentration of an agent which blocks the apoptosis protecting effects of the protease inhibitor,
- determining the degree of apoptosis induced in said samples, and
- identifying the anti-cancer treatment as one, the efficacy of which is dependent on presence or absence of apoptosis-inhibiting protease inhibitors if 1) the degree of apoptosis induced in the samples from the first population of cells is significantly higher in the presence of the agent, and 2) the degree of apoptosis induced in the samples from the second population of cells is not significantly higher in the presence of the agent.

39. A method for identifying an anti-cancer treatment the efficacy of which is not dependent on presence or absence of apoptosis-inhibiting protease inhibitors, the method comprising
- providing a first population of malignancy-derived cells that are +/+ or +/- for said protease inhibitor,
- providing a second population of malignancy-derived cells that are -/- for said protease inhibitor,
- subjecting samples of said first and second populations of cells to substantially the same anti-cancer treatment in the absence and presence of an effective concentration of an agent which blocks the apoptosis protecting effects of the protease inhibitor,
- determining the degree of apoptosis induced in said samples, and
- identifying the anti-cancer treatment as one, the efficacy of which is not dependent on presence or absence of apoptosis-inhibiting protease inhibitors if 1) the degree of apoptosis induced in the samples from the first population of cells is not significantly higher in the presence of the agent, and 2) the degree of apoptosis induced in the samples from the second population of cells is not significantly higher in the presence of the agent.

40. Use of a blocker of a protease inhibitor for the preparation of a pharmaceutical preparation for enhancing the effect of anti-cancer therapy.

41. The use according to claim 40, wherein the protease inhibitor is selected from the group consisting of the protease inhibitors defined in claim 4.

42. The use according to claim 40 or 41, wherein the blocker is selected from the group consisting of the blockers defined in claim 5.

43. The use according to any one of claims 40-42, wherein the anti-cancer therapy comprises subjecting the patient to conditions that induce cancer cell death by apoptosis.

44. The use according to any one of claims 40-43, wherein the blocker induces a preferential increase in apoptosis in the malignant cells compared to non-malignant cells when the patient is subjected to the anti-cancer therapy.

45. The use according to any one of claims 40-44, wherein the anti-cancer therapy is selected from the group consisting of radiation therapy, endocrine therapy, and cytotoxic or cytostatic chemotherapy, or a combination thereof.

46. The use according to claim 45, wherein the cytotoxic or cytostatic chemotherapy is selected from the group consisting of treatment with the agents defined in claim 1.

47. The use according to claim 45, wherein the endocrine therapy is selected from the group consisting of treatment with the agents defined in claim 15.